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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/980,557 | 12/04/2001 | Pasqualino Loi | LOI=1 | 8858 |

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| EXAMINER | |
|---|---|
| CROUCH, DEBORAH | |
| ART UNIT | PAPER NUMBER |
| 1632 | |

DATE MAILED: 08/11/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/980,557 | LOI ET AL. | |
| | Examiner | Art Unit | |
| | Deborah Crouch, Ph.D. | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *21 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *39-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicant's arguments filed May 21, 2004 have been fully considered but they are not persuasive. The amendment has been entered.

Deborah Crouch, Ph.D. Art Unit 1632 has been assigned this application for examination. The examiner's contact information is in the last paragraph of this office action.

Claim 49 contains a misspelled word: "granulose" should be "granulosa."

Applicant's cancellation of claims 34-36 has rendered the rejections made under 35 U.S.C. 102 (b) moot.

Claims 41-44 would be allowable if rewritten in independent form. Presently, claims 41-44 are objected to for depending from rejected claims.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 39, 40, 47, and 49-64 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process of reconstructing a nonhuman mammalian embryo comprising transferring into an enucleated metaphase II oocyte a donor cell or donor cell nucleus of the same species as the oocyte where the chromatin within the nucleus had been subject to thermal denaturation prior to transfer to the oocyte, does not reasonably provide enablement for the process where the chromatin had been denatured by any other process. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification discloses denaturation of donor cell chromatin by heat, ph change, alterations in ionic strength of buffers and/or chromatin denaturing agents, the specification

only provides sufficient guidance on heat denaturation for enablement of the claimed invention. The specification, any evidence of record or any search of the relevant art shows readily available methods to denature chromatin while still leaving the chromosomal DNA intact sufficient for methods of nuclear transfer. Since nuclear transfer requires a full complement of genetic material to guide the formation of a cloned mammal, the chromosomes within the nucleus must be intact. Alterations in pH for example, hydrolyze the phosphodiester bonds of the DNA molecules and thus would destroy chromosomal material. The conditions "change in ionic strength" and "chromatin denaturing agents" are not enabled because the specification does not provide any guidance as to changes in ionic strength or chromatin denaturing agents that do not destroy the chromosomal material but permit the enhanced rate of blastocyst formation and pregnancy rates. Fundamentally, applicant has developed a new method of treating donor nuclei prior to nuclear transfer, but the specification fails to provide guidance for the breath of "denaturing conditions" other than the specifically exemplified heat method. The specification does not discuss any ionic strength or ranges of ionic strength that would be applicable to the claimed invention, nor do they provide any discussion of "chromatin denaturing agents" that would alter the nucleoprotein structure of the chromatin to reach the enhanced rates of embryo formation and pregnancy. There is no evidence that the skilled artisan would know where to begin the implementation of the claimed invention given its breadth, much less ever reach the claimed invention.

Even though, never argued, applicant's process for reconstructing a nonhuman mammalian embryo has a readily apparent use for the study of embryological processes and mechanisms. This use is based upon the fact that applicant achieved a higher rate of embryo formation and a higher rate of pregnancy. However, applicant has not demonstrated any effect of the claimed process on actual rates of live birth.

Thus, at the time of the instant invention, the skilled artisan would have had to engage in an undue amount of experimentation without a predictable degree of success to make and use the invention of the claims.

Claims 48 and 65-68 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 48 is drawn to a process for reconstructing an embryo where the donor cell is non-living that is dead or dying. Dead or dying cells have chromosomal degradation and will not successfully produce a developing embryo. While reprogramming might remodel chromatin to a very early embryonic state, there is no evidence of record or in the art that reprogramming can successfully re-form degraded chromosomes.

Claims 65-68 are drawn to a process for generating a nonhuman mammal comprising producing a reconstructed embryo produced by transferring a donor cell or a donor cell nucleus where the cell or nucleus has been subjected to denaturing conditions prior to transfer, developing the embryo to a blastocyst, transferring the blastocyst to a suitable animal, causing the blastocyst to develop to term and further breeding the resulting animal.

This claim is not enabled because the specification clearly teaches that the pregnant sheep lost their fetuses. While it can be agreed that certain animals and ungulates in particular, have been cloned, the present method does not appear to have a predictable outcome of live births. This is especially noteworthy as the method increases embryo formation, implantation rates and pregnancy rates. It is documented in the arena of nuclear transfer/cloning that pregnancy does not necessarily mean live births. Tiger clones were lost well after pregnancy was established, as were domestic cats and rabbits. *Korean Now* (May

31, 2003) reports that a tiger became pregnant with a cloned tiger embryo made using a cow embryo, but that the tiger had a miscarriage. *The Wall Street Journal* (March 19, 2002) reports that an effort to clone a Siberian tiger but that cloning attempts have failed, although a tiger embryo was produced by nuclear transfer using a bovine oocyte. Robert Wall of the USDA is quoted as stating that despite years of effort, "[w]e're in the same bind that we've always been in. A majority of [would be clones] do not make it to term." (Pennisi, page 1722, col. 1, parag. 2, lines 9-14). Pennisi and Vogel state, "even when an embryo does successfully implant in the womb, pregnancies often end in miscarriages" (Pennisi, page 1722, col. 1, parag. 3, lines 16-18). The case with rabbits indicates that obtaining an embryo by nuclear transfer does not translate into a cloned rabbit. While many cloned rabbit embryos can be made, they abort upon transfer to surrogate mothers, and in 2000, there had not been any successes in cloning rabbits (Pennisi, page 1725, col. 2, parag. 3). With primates, two cloned monkeys were produced, but there have been no subsequent successes in primate cloning (Pennisi, page 1726, col. 2, line 6 to col. 3, line 3). With regard to cats, one cloned cat has been produced, but given the difficulty in the art to produce a cloned cat and the lack of producibility as stated above, the cloning of cats is unpredictable. Two attempts to implant cat eggs or reconstructed embryos failed, providing for an unpredictable outcome for cat cloning (Pennisi, page 1726, col. 2, parag. 3, lines 4-5). Others have reported establishing pregnancies but no report of a cloned cat being born (Pennisi, page 1726, col. 2, parag. 3, lines 5-9 and 11-12). As the authors state, establishing pregnancies is only part of the problem and is not a guarantee of a cloned mammal being produced (Pennisi, page 1726, col. 2, lines 9-11). Given the recognized the low birth rate in nuclear transfer procedures, which applicant states their invention overcomes, an inability to carry to term is a significant issue. Given that the claimed method denatures the chromatin, this denaturation could have caused damage to

chromosomes or genes needed for fetal development but not embryonic growth and implantation. The evidence of record does not make clear that live births occurred as a result of the claimed method.

Further, as stated by the previous examiner, the art at the time of filing recognized that cross-species nuclear transfer procedures did not result in development to term. It was known at the time of filing, that cross-species nuclear transfer was unpredictable in both embryo and term development. Meirelles demonstrate that methods of nuclear transfer where the nuclear material of *Bos indicus* is inserted into the oocyte of *Bos taurus* produces calves comprising the nuclear material of *Bos indicus* and the mitochondria of *Bos taurus*. Meirelles *et al.* teach that previous attempts to use the *Bos* oocyte as hosts for nuclear transfer from unrelated species allowed development to the blastocyst stage however conclude that incompatibility among the nuclear and mitochondrial genetic systems is responsible for the early arrest. Meirelles *et al.* also point to similar failures using *Mus caroli* and *Mus musculus* citing Dominko *et al.* discussed in length in the previous office action. Meirelles *et al.* conclude that in light of their results and the failures of the prior art, that nuclear transfer across subspecies barriers is possible. (see Meirelles, pp. 351-355). The present specification encompasses nuclear transfer (cloning) when the nucleus is of one species and the oocyte is of another species. This clearly lacks predictability given the teachings of Meirelles. Further, in the production of sheep goat chimeras, there were biases towards chimeras whose genotype and phenotype was most like that of the recipient, and that the successful production of chimeras resided in the neutralization of incompatibility between the chimeric embryo (Fehilly et al (1985), page 221, parag. 1). This is also an unpredictable feature of the claimed invention as an embryo of one species implanted into a surrogate mother of another species is unlikely to develop given the teaching of Fehilly. The specification does not provide guidance on producing cross-species embryo or animals, nor

how to overcome the unpredictable nature of cross-species cloning. Guidance is not provided in the present specification to overcome this cross-species barrier. While nuclear transfer using sheep cells and oocytes, bovine cells and oocytes, or goat cells and oocytes might result in live births in certain methodologies, it was unpredictable at the time of filing that sheep x bovine, sheep x goat nuclear transfer procedures, and the like combinations would lead to live births. As further evidence that cross-species nuclear transfer was not enabled at the time of filing, applicant is referred to the discussion above concerning the inability for a tiger embryo produced by nuclear transfer using a bovine oocyte as recipient cell, failed.

Thus, at the time of the instant invention, the skilled artisan would have needed to engage in an undue amount of experimentation to make and use the claimed invention.

Applicant's arguments filed May 21, 2004 are addressed to the extent that they pertain to the new rejection.

Applicant argues that methods of nuclear transfer were known for many species at the time of filing. Applicant argues that the invention is to maximize the number of successful implants. Applicant argues that the rate of cloning success is limited by difficulties in reprogramming chromatin, citing Dinnyes. Applicant argues that the present invention solves the problem by providing a preliminary step to add to nuclear transfer protocols to induce the successful development of embryos in vitro and once transferred into a recipient. These arguments are not persuasive.

The evidence of record does point to an improved rate of embryo development and embryo implantation into the uterine wall of recipients. However, the implanted embryos did not develop to term and thus the use of the method as an improvement in the production of cloned animals is questioned. It is very well that more embryos are made, that more embryos implant and that more embryos begin dearly development in the uterus, but the

fact that all pregnancies were aborted is strong indication that the method interferes with late-term development.

Applicant argues that inter-species nuclear transfer will also be improved by the denaturing process. This argument is not persuasive.

The art at the time of filing clearly taught that cross-species nuclear transfer does not yield term births. Thus, when cross-species nuclear transfer is combined with the present invention, which is also shown not to result in term births, no improvement as argued is achieved. More evidence is needed to substantiate applicant's arguments regarding cross-species nuclear transfer.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 39, 45, 46, 50-54 and 56-58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 45 is confusing. Chromatin with in a cell is organized into chromosomes even when the chromosomes are heterochromatic. It is not clear what applicant is trying to claim that is different from claim 39.

Claim 46 is confusing. The donor cell is one cell. One cell can only be collected from a single individual.

Claim 50 is confusing. Dead or dying cells will not contribute to nuclear transfer. Dead and dying cells are pinocytotic and have chromosomal degradation.

Claim 52-54 are confusing as to the meaning of "includes." Does applicant mean "comprises," so that the genetic modification can be any number of modifications at one time?

Claim 54 is further confusing as to the meaning of "homologous group." A homologous group of what?

Claims 56-58 are confusing as to the meaning of "carried out on." Does applicant the denaturing treatment alters nucleoprotein assembly or alters the nucleus? Further, the specification discloses that the denaturation alters the chromatin structure within the nucleus. Applicant's claims are further confusing as to the location of the chromatin or nucleoprotein structure during the denaturation.

The claims are free of the prior art. At the time of the present invention, the prior art did not teach or suggest a process for reconstituting an animal embryo or a process for generating an animal as claimed where the donor cell or donor cell nucleus is denatured prior to insertion into the recipient oocyte.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 571-272-0727. The examiner can normally be reached on M-Th, 8:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on 571-272-0408. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Deborah Crouch, Ph.D.
Primary Examiner
Art Unit 1632

August 9, 2004